REMARKS

Entry of the foregoing amendments, reconsideration and re-examination of the subject application, as amended, pursuant to and consistent with 37 C.F.R. §1.112, and in light of the remarks which follow, are respectfully requested.

By the present amendments, previous Claims 21-40 are cancelled in favor of new Claims 41-55. The claims are believed to overcome all of the outstanding rejections. Specific support for the use of the subject antibodies for treatment by blocking the B7.1/CD28 interaction finds support at pages 11-12 of the subject application, et seq.

Turning now to the Office Action, Claims 21, 23-25, 29-31 and 35-37 stand rejected as not being enabled by the teachings of this application. The Examiner purports that the in vitro data in the specification which substantiates that anti-B7.1 antibodies having the recited epitopic specificity act as effective immunosuppressants may not correlate to in vivo efficacy, particularly that the subject antibodies can be used for treating an autoimmune disease. This rejection is respectfully traversed on two bases.

First, the independent claim has been revised to recite that the subject antibodies are used to block the B7.1/CD80 interaction in subjects in need of such treatment. This should obviate the enablement rejection as it has been adequately demonstrated that antibodies according to the invention inhibit the interaction of B7.1 and CD80 and thereby function as effective immunosuppressants. This is analogous to the therapeutic claims relating to the use of B7 antagonists in U.S. Patent 5,885,579 wherein the U.S. Patent Office granted claims directed to the use of B7 antagonists to treat immune diseases involving the interaction of T cells with B7 positive cells by regulating such interaction by the use of B7 ligands. Thus, the Patent Office has conceded the fact that B7-specific ligands may be used to treat immune diseases by inhibiting the interaction of T cells (which express CD28) with B7 positive cells.

Additional evidence that the subject antibodies are effective in vivo can be found in a Declaration by Darrell Anderson also submitted during prosecution of related application, U.S. Serial No. 08/746,361 also being prosecuted by the subject Examiner.

Therein, Dr. Anderson attests to the functional properties of the subject antibodies in mixed lymphocyte reactions that demonstrate that antibodies according to the invention inhibit B7.1 with CD28, and block IL-2 production when B7.2 antigen was present.

The in vivo immunosuppressant activity of antibodies according to the invention, especially for treatment of autoimmune diseases is evidenced by a draft manuscript entitled

"Single-Dose Treatment of Moderate to Severe Psoriasis with a PRIMATIZED® Anti-CD80 Antibody." This manuscript shows that administration of an antibody according to the invention to subjects with moderate to severe plaque-type psoriasis resulted in improvement of psoriatic symptoms as measured by changes to the mean total PASI score (a standard scale for measuring the clinical prognosis of psoriatic patients).

In particular, these clinical studies showed an improvement in the size of plaques and decreased numbers of $CD3^+$ cells, $CD8^+$ cells, and Ki-67^+ cells. Thus, there is in vivo clinical data that substantiates that antibodies according to the invention function as effective therapeutics, especially for treatment of autoimmunity. Withdrawal of the §112 enablement rejection is therefore respectfully requested.

Claims 21-40 also stand rejected as requiring the use of specific cell lines that need to be deposited. This rejection should be moot as the claims are now directed to antibodies that have the epitopic specificity of antibodies which contain specific variable heavy *and* light sequences. As it is the variable sequence that determines epitopic (binding) specificity there is no need for any deposit of cell lines. Indeed, one skilled in the art could produce antibodies by recombinant methods that possess the subject variable regions.

Withdrawal of this rejection is therefore respectfully requested.

Claims 21-40 were rejected under 35 USC §112 second paragraph. This rejection should be moot as the claims no longer refer to particular antibodies by name.

Claims 21-23, 26, 29, 30, 32, 35 and 38 are rejected based on 35 USC §103 over Linsley et al. and de Boer et al. This rejection is respectfully traversed on the basis that neither reference teaches or suggests the use of anti-B7.1 antibodies possessing the recited epitopic specificity as therapeutics.

Applicants acknowledge with respect thereto, at the outset that antibodies to B7.1 were known prior to the invention and also that techniques for generating antibodies to a known antigen were well known. However, notwithstanding these admissions this does not support a conclusion that antibodies as set forth in the claimed methods were obvious.

Indeed, as recognized by the Examiner neither de Boer or Linsley teach antibodies having the unique binding interaction of the subject antibodies. In this regard, the Examiner indicates that Linsley suggests such antibodies because the patentees indicate that anti-B7 antibodies can be used to block interaction of B7 cells with CD28 *"or"* CTLA-4 expressing cells. (Col. 15, para 7 of Linsley). However, this conclusion is unsustainable. As previously

argued, at best the references cited by the Examiner including Linsley et al. arguably would render the claimed invention "obvious to try." However, this is not the appropriate obviousness standard. In particular, the rejection is unsubstantiated as neither reference supports a conclusion that the production of antibodies possessing the recited binding interaction would have been "reasonably expected." The outcome is not reasonably expected because of the unique binding interaction of the subject anti-B7.1 contribution, which was unknown prior to the present invention. Based on this unique binding interaction, the subject antibodies do not function equivalently to the prior art antibodies and moreover are uniquely and exquisitely suited for use as immunosuppressants and particularly for treating T cell mediated autoimmune disorders such as psoriasis. This is supported by the prior declaration of Dr. Anderson and the second declaration by Dr. Anderson submitted herewith.

Most especially, the Examiner's obviousness determination ignores the fact that all other known reported anti-B7.1 antibodies cross-react with CTLA-4. The Examiner's conclusion further ignores the high degree of conservation of B7 antigens in different species and particularly in humans and cynomolgus monkeys. The fact that Applicants were able to generate anti-B7 antibodies in cynomolgus monkeys of adequate binding affinity to be useful as therapeutics was itself an unexpected outcome. That such antibodies would also fortuitously bind to an epitope the existence of which was heretofore unknown is truly surprising. The Examiner is again respectfully referred to the two declarations by Dr. Anderson in support of this argument.

As established by the earlier Affidavit by Dr. Anderson, the subject antibodies exhibit distinct binding characteristics vis-a-vis other reported anti-B7.1 antibodies, and particularly those disclosed in the cited Linsley and de Boer et al. Patents. Particularly, the prior art antibodies inhibit the binding interaction of B7.1 with CTLA-4. Whereas the inventive antibodies do not.

Contrary to the Examiner's assertions, it could not have been reasonably predicted that an antibody possessing the binding properties of the invention could have been obtained. Indeed, it was entirely possible that the epitopes responsible for B7.1/CD28 binding and B7.1/CTLA-4 binding could have been proximate to one another.

Also, it would not have been obvious that an antibody to B7.1 that selectively inhibits the B7.1/CD28 interaction, but not the interaction of B7.1/CTLA-4, would be therapeutically effective. Indeed, it would be expected that they might possess very different functional

characteristics and that this might affect the therapeutic value of such antibodies. Indeed, this has proved to be the case.

Particularly, it should be emphasized that only blocking the B7.1/CD28 interaction could not have been reasonably predicted to yield therapeutic benefits vis-a-vis blocking the B7.1/CTLA-4 interaction. This could have been predicted because of the biological effects of CTLA-4 and the differences in manner and timing of B7.1 and B7.2 expression during T cell activation. The prior art antibodies of de Boer et al. and Linsley et al. inhibit the interaction of CTLA-4 (CD152) which is a high affinity counter-receptor for both CD80 (B7.1) and CD86 (B7.2). It is further known that B7.1 or B7.2 binding to CTLA-4 initiates an intracellular signaling cascade that down regulates T cell activation that counteracts CD28-mediated co-stimulation.

However, while the co-stimulatory roles of B7.1 and B7.2 are similar, their actual role in T cell activation, and particularly in T cell diseases such as psoriasis was uncertain. While both of these B7 antigens are upregulated on activated T cells, their temporal expression, density and kinetics are differentially regulated.

As explained in the draft manuscript attached to Dr. Anderson's affidavit provided herewith, because CD86 (B7.2) is expressed constitutively and upregulated quickly, it would be expected a to play a more important role in the activation of T cell immune responses than CD80 (B7.1). By contrast, CD80 binds more strongly to CD152 (CTLA-4) and it is hypothesized based therein that its biologically relevant role may be to terminate activation via CD152. However, this had not been established as of the filing date of this application. Consequently, it could *not* have been predicted that an antibody which inhibits the B7.1/CD28 interaction but not the B7.1/CTLA-4 (CD152) interaction would be a useful therapeutic agent. Unexpectedly, it has been shown in vitro and in vivo that antibodies according to the invention exhibit distinct functional properties and that this translates to therapeutic efficacy.

Particularly, and as supported by the declaration by Dr. Anderson, the subject antibodies when utilized in a mixed lymphocyte reaction inhibit IL-2 production in the presence of B7.2. By contrast, the comparative prior art anti-B7.1 antibody, reported by Nickoloff et al. (L307.4), which inhibits the interaction of B7.1 with CTLA-4 (unlike the inventive antibodies) did not inhibit IL-2 production under the same conditions. It could not have been predicted that merely blocking B7.1/CD28 interaction would yield this result.

These functional differences are not suggested by the prior art and provide additional evidence that the inventive antibodies are not equivalent nor are they obvious vis-à-vis previous anti-B7.1 antibodies. This could not have been predicted given the significant role of CTLA-4 during regulation on B7.1 and B7.2 expression. Rather, as B7.2 was thought to play a more significant role, it would have been reasonably expected that blocking only B7.1/CD28 interaction would not be sufficient to significantly effect T cell function.

It is respectfully submitted that the binding differences between the subject antibodies vis-à-vis the prior art, coupled with the different functional characteristics that result from these binding differences provide convincing evidence in favor of the patentability of the subject anti-B7.1 antibodies over the prior art. Quite clearly these differences substantiate a conclusion that the subject antibodies are not equivalent to previous anti-B7.1 antibodies including the reference antibodies relied upon by the Examiner.

While these in vitro functional and binding differences are believed to be sufficient, Applicants further submit that the subject claims should be allowed as it could not have been reasonably expected that antibodies possessing the subject unique binding interaction and in vitro properties would be suitable for clinical usage. Particularly, Applicants have clinical data which substantiates that antibodies according to the invention may be used to treat T cell disorders, particularly psoriasis.

Applicants have shown in preliminary psoriasis human clinical studies using IDEC-114 that the subject anti-B7.1 antibodies appear to be safe, well-tolerated, and clinically effective in treating psoriasis. Particularly, an antibody according to the invention was shown to effectively reduce psoriatic plaques and to yield improved clinical scores in psoriasis patients. Thus, it has been surprisingly shown that selectively blocking the B7.1:CD28 interaction is an efficient means of immunoregulation in the context of treating T cell mediated diseases such as psoriasis.

For the reasons already enumerated, it could not have been predicted that an antibody that blocks the B7.1/CD28 interaction and not B7.1/CTLA-4 would be therapeutically effective as CTLA-4 was known to play a significant role in T cell down regulation. The significant role of CD152 as a preferred negative regulator of T cell activation is supported by the fact that CD152 deficiencies result in profound lymphoproliferative disorders and early death.

Thus, the subject antibodies are patentable over previous anti-B7.1 antibodies as they possess clinical properties that could not have been reasonably predicted from their binding properties.

This further should be probative of the novel and non-obvious nature of the claimed invention which claims the use of such antibodies as therapeutic especially as the Examiner seemingly questioned whether it could be reasonably predicted that the different binding interaction of the subject antibodies will correlate to any significant functional difference and clinical efficacy.

In fact, Applicants have now provided probative evidence in the §132 Declaration and Exhibit (draft manuscript attached thereto) that antibodies according to the invention function very differently in vitro and that antibodies according to the invention are clinically effective.

Withdrawal of the §103 rejection based on Linsley et al. and de Boer is therefore respectfully requested.

This rebuttal is supported by the prior-discussed affidavit of Darrell Anderson, Ph.D. enclosed with this Reply. Based thereon, withdrawal of the §103 rejection based on Linsley et al. and de Boer et al. in view of Nickoloff et al. and Newman et al. is respectfully requested.

Based on the foregoing, this application should be in condition for allowance. A Notice to that effect is respectfully solicited.

Respectfully submitted,
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